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In Vivo, noninvasive glucose monitoring with optical heterodyne polarimetry in a range of 50 mg/dl ~ 100 mg/dl

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ABSTRACT

An amplitude sensitive optical heterodyne polarimeter was setup in order to monitor noninvasively the aqueous glucose concentration in rabbit's eye. A range of the blood glucose from 35 mg/dl to 135mg/dl was measured *in vivo* by biological glucose assay (BGA), while the optical rotation of the aqueous glucose was measured by a polarimeter simultaneously. The experimental results showed the consistence between these two independent measurements. There was no time delay between the blood glucose and the aqueous glucose when the blood glucose was descending after the insulin was injected. It was in contract to a 10 minutes time delay when the blood glucose was ascending. The detection sensitivity of the polarimeter was 4 mg/dl in the measurement.

Key words : heterodyne, polarimeter, glucose, noninvasive

1. INTRODUCTION

Different techniques have been used to monitor glucose concentrations noninvasively¹⁻⁵. The reduced scattering coefficient of the tissue, which shows a correlation with the glucose concentration^{3,5}. However, the experimental result of measuring μ'_s *in vivo* showed a 73% confidence level in noninvasive glucose monitoring by the diabetic volunteers. Physiological interference such as temperature change, blood flow, and tissue heterogenetics can degrade the performance of the detection. The polarimeter in the photometric technique used a Faraday modulator to generate the polarization modulation of the incident laser beam before the test sample^{2,3}. A Faraday rotator and an analyzer were used to null the rotation of the polarization vector due to the glucose sample and then to sense the optical rotation angle in terms of the dc voltage applied to the Faraday compensator. The sensitivity of that method showed a 10-mg/dl detection sensitivity of the glucose concentration in the double distilled water and the cell culture medium with a 1-cm-wide optical path. The aqueous humor in the eye is the window for measuring the blood glucose that relies on the measurement of the optical rotation angle of the aqueous glucose (see Fig. 1). The measurement is based

on the result of a high correlation between the blood glucose and the aqueous glucose according to the observations made by March *et al*⁶ and the fact that the optical rotation angle of the glucose is linear proportional to its concentration. The aqueous protein, which is also an optical active substance, has a very low concentration (0.013g/100ml) in the aqueous humor owing to the diffusion filtering processing across the semi-permeable membrane. The optical rotation caused by the other substances in the aqueous humor can be ignored^{6,7}. The measurement of the concentration of the optical active medium is related to the optical rotation angle θ_m by

$$[\alpha]_{\lambda,PH}^T = \frac{\theta_m}{CL} \quad (1)$$

where $[\alpha]_{\lambda,PH}^T$ is the specific rotation of a molecule in the medium^{2,4}, C is the concentration, and L is the optical path length of the test medium. Chou *et al*⁴ proposed a different technique based on an optical heterodyne polarimeter in which a Zeeman laser in conjunction with a Glan-Thompson analyzer was used. The glucose concentrations can be measured in terms of the optical rotation of a linear polarized light in the aqueous humor by measuring the amplitude of the heterodyne signal. Blood glucose in the range of 100-200 mg/dl of New Zealand white rabbits have been measured in terms of the optical rotation after the rabbit was anesthetized. The result was consistent with the blood glucose by biological glucose assay (BGA). However, a 30 minutes time delay⁽⁴⁾ between the blood glucose and the aqueous glucose was observed. It was caused by the blood glucose diffusing slowly into the aqueous humor through a semi-permeable membrane⁷. In this paper, a range of low concentrations of the blood glucose (35-135 mg/dl) of healthy New Zealand white rabbits were measured *in vivo* by BGA. Meanwhile, the optical rotation of the aqueous glucose was monitored by the polarimeter simultaneously. The experiment showed the consistence between these two independent measurements. There was no time delay between the blood glucose and the aqueous glucose after the insulin was injected when the blood glucose was descending. It was in contrast to a 10 minutes time delay that the glucose was ascending 45 minutes after the insulin was injected.

2. PRINCIPLE

An amplitude-sensitive optical heterodyne polarimeter was set up as shown in Fig. 2. A Zeeman laser that consists of two orthogonal linearly polarized states with different temporal frequencies and one Glan-Thompson analyzer was used. The optical heterodyne signal was generated when the laser beam was passing through a Glan-Thompson analyzer at a fixed azimuth angle. The laser was incident on the optical active medium, the aqueous humor, that rotates the P and S states by angle θ_m simultaneously (see Fig. 3). When the laser beam passed the analyzer, where the azimuth angle of the analyzer was set at θ_s , the output intensity is

$$I_s = a_1 a_2 \sin 2(\theta_s + \theta_m) \cos(\Delta\omega t) \quad (2)$$

where a_1 and a_2 are the amplitudes with respect to the two eigenmodes from the laser. If $|0^\circ < \theta_s + \theta_m < 5^\circ|$,

then Eq. (2) can be expressed as

$$I_s \cong 2a_1 a_2 (\theta_s + \theta_m) \cos(\Delta\omega t) \quad (3)$$

If we assume that $I_0 = 2a_1 a_2 \theta_s \cos(\Delta\omega t)$ when the zero concentration of the glucose is tested, the difference intensity of the non-zero concentration is $|\Delta I| = |I_s - I_0| = 2a_1 a_2 \theta_m$. It means that the variation of the optical rotation angle equals to $2a_1 a_2 \theta_m$. The detection sensitivity of the optical rotational angle is then amplified by a factor $2a_1 a_2$.

3. EXPERIMENTAL SETUP AND DISCUSSION

Figure 2 shows the configuration of the experimental setup in which an HP5519 Zeeman laser was used. The laser beam consisted of two eigenmodes with different temporal frequencies in 1mW output power. The frequency difference between the two orthogonal polarized waves, the P and the S waves, was 2.6 MHz. The output wavelength of the Zeeman laser was 632.8 nm. A Glan-Thompson analyzer was adopted in this experiment to generate the 2.6-MHz heterodyne signal. Two healthy New Zealand white rabbits were tested successfully. Their weights ranged from 3.0 to 4.0 kg. At the beginning, Changzine and Imalgene were injected into a rabbit (I. M.) to anesthetize the rabbit. A blood sample from the artery of the rabbit ear was then measured by BGA every 2 minutes. A 0.65 I.U/kg Humulin (Humulin R, Lilly, USA) was then injected into the artery right after the first sampling of the blood sample. Then, the aqueous glucose was monitored. The blood glucose were checked every 2 minutes in order to follow the rapid response of the blood glucose⁷. Two independent measurements were matched under the same time base as shown in Fig. 4(a). The magnitude of the aqueous glucose has been scaled linearly by fitting the data points in the descending curve of the blood glucose after Humulin was injected. From the experimental results, we can see that there is not any time delay when the blood glucose was descending. In contrast, once the blood glucose started to ascend, the aqueous glucose followed the blood glucose 10 minutes time delay as shown in Fig. 4(a). The delay time was caused the blood glucose slowly penetrated the semi-permeable membrane from the artery into the aqueous humor⁸. Figure 4(b) shows the same response of the aqueous glucose of the second rabbit after the Humulin was injected. Similar response between the blood glucose and the aqueous glucose was observed in Fig. 4(a) and Fig. 4(b). Therefore, the proposed glucose monitoring system successfully monitored the blood glucose through the aqueous glucose in a range of 35~135 mg/dl without any time delay.

A Zeeman laser in conjunction with a Glan-Thompson analyzer to form an optical heterodyne polarimeter is able to measure the aqueous glucose from 35 mg/dl to 220 mg/dl⁴. A time delay between the blood glucose and the aqueous glucose depends on the situation of the ascending or descending of the blood glucose. The detection sensitivity as well as the linearity of the measurement proves that this method is able to monitor the blood glucose *in vivo*, noninvasively and accurately. The signal fluctuation of the polarimeter can be suppressed by keeping the eyeball steady during the measurement or using a pulse laser to measure the aqueous glucose.

In conclusion, When the equilibrium between the aqueous glucose and the blood glucose is maintained. The aqueous glucose equals to the blood glucose. There is no delay time between the blood and the aqueous glucose to be considered. This proposed method has been proved to be effective in achieving the goal of monitoring the blood glucose in vivo and noninvasively.

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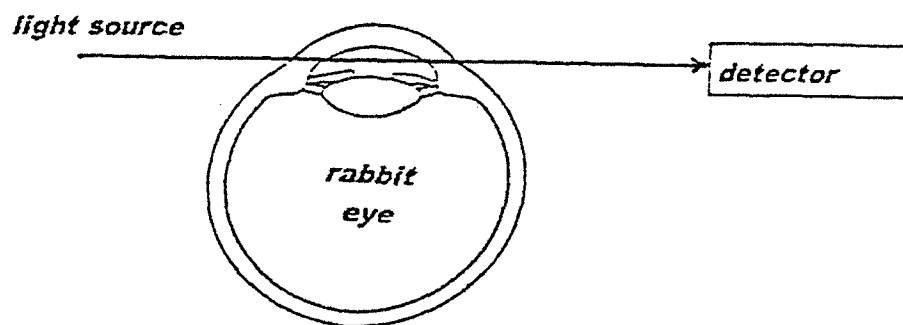


Fig. 1

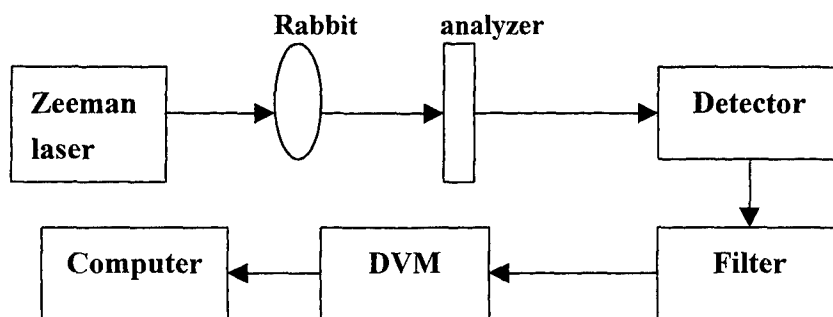


Fig2.

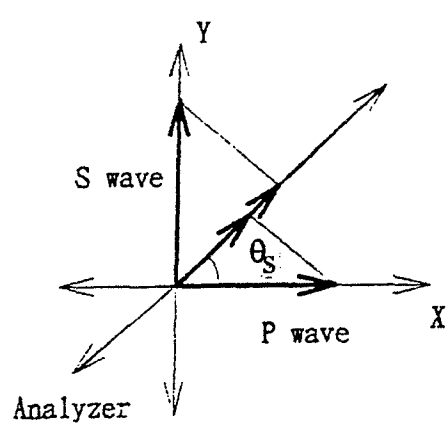


Fig3.(a)

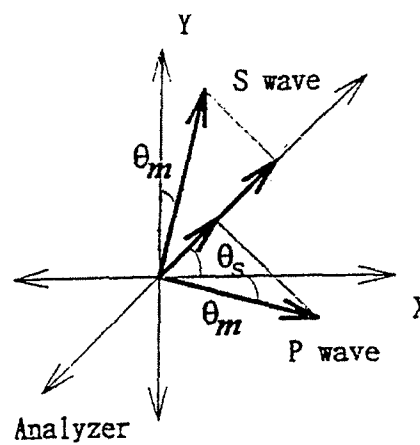


Fig3.(b)

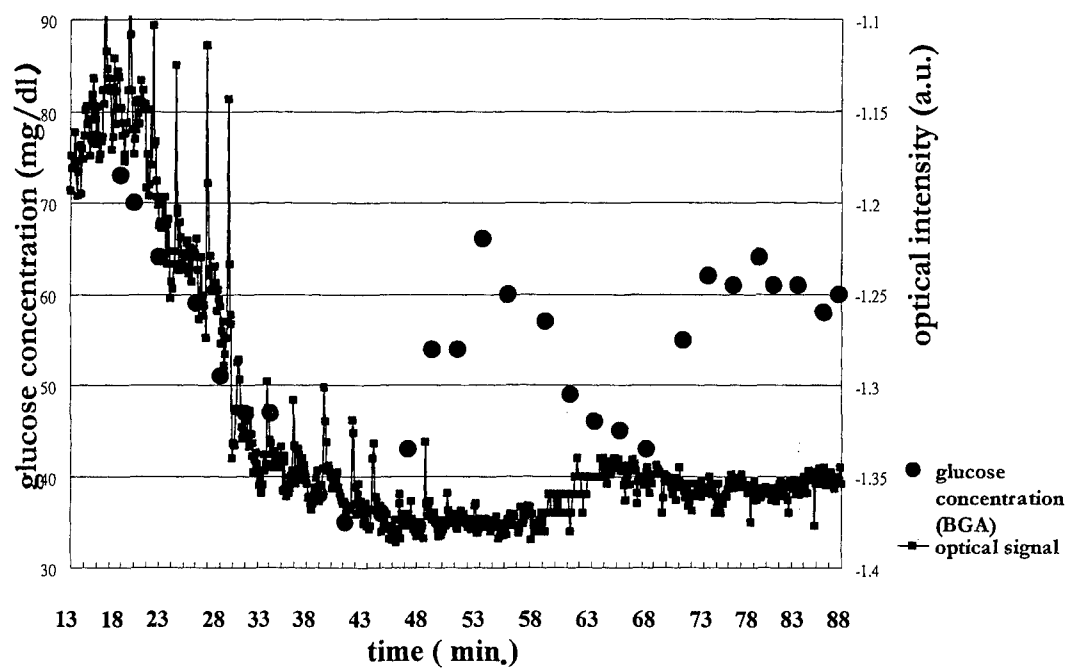


Fig.4(a)

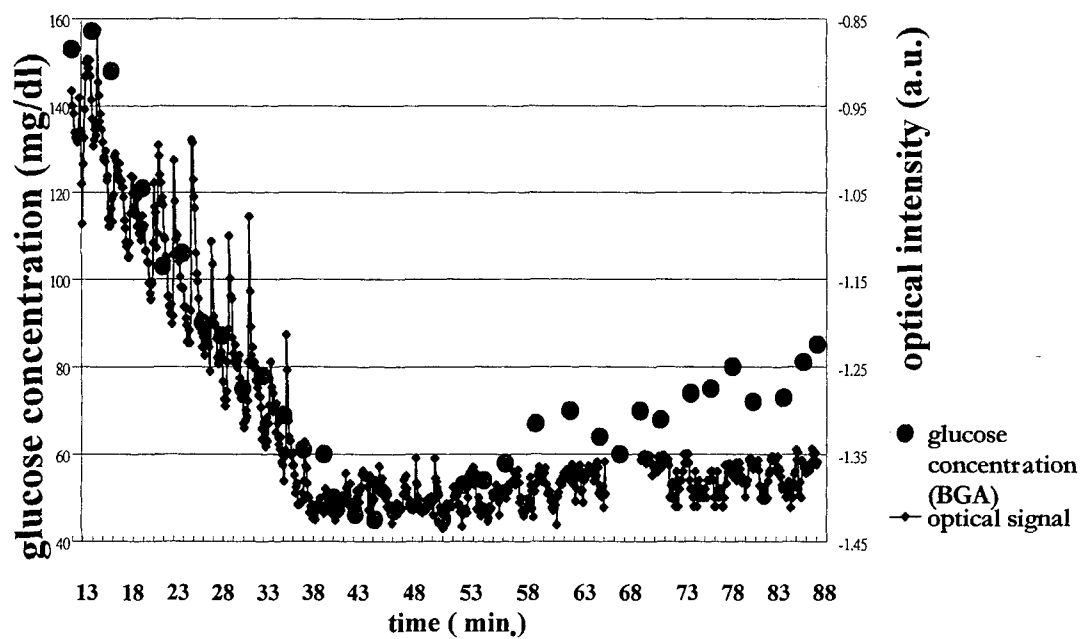


Fig.4(b)